Margarita Salas, a pioneer of molecular biology in Spain and a role model for female scientists

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Margarita Salas, an exceptional scientist, a pioneer of molecular biology in Spain, and a role model for Spanish female scientists and for several generations of researchers, passed away on November 7 in Madrid, aged 80. She retained her passion for science right up to her passing, working tirelessly in her laboratory at the Centro de Biología Molecular Severo Ochoa (CBMSO), where she served as Professor *Ad honorem*.

Her encounter with Severo Ochoa at a conference in Asturias in the summer of 1958 convinced her to pursue a career in biochemistry. Ochoa subsequently became her mentor and role model in many aspects.

A firm defender of a high-quality basic research, she personified the words of the Nobel laureate Ochoa: "A country without research is a country without development." She emphasized the need to promote basic research, the basis for the development of a country and the source of many discoveries that benefit mankind. She put this belief into practice throughout her entire scientific career, focusing on the study of the bacteriophage *Phi29*, more recently known as *Salasvirus*.

Specifically, her discoveries relating to the mechanisms of action of the DNA polymerase of phage *Phi29* revolutionized molecular genetics, promoting the development of simple techniques for the amplification of DNA from small samples.

This discovery formed the basis of several international patents with important applications in biotechnology and biomedicine. Indeed, the first of these patents has generated more benefits for the CSIC than any other. In the years that the patent was active (2003–2009), it accounted for more than half of the total income generated by CSIC patents.

Doctoral thesis at the CIB (1961–1964)

Margarita Salas, born in Canero (Asturias) in 1938, graduated in Chemical Sciences at the Universidad Complutense de Madrid, and began her scientific career at the CIB, where she completed her doctoral thesis on carbohydrate metabolism between 1961 and 1964, under the supervision of Alberto Sols. During this period, she made her first scientific discovery: the enzymatically catalyzed anomerization of glucose-6-phosphate.

She arrived at Alberto Sols' laboratory recommended by Severo Ochoa, with the promise that upon completing her doctorate she could pursue postdoctoral research in Ochoa's laboratory at New York University School of Medicine, where she subsequently worked between 1965 and 1967. She was accompanied to New York by her

Margarita Salas and Eladio Viñuela in their CIB laboratory in 1962.

husband, the researcher Eladio Viñuela. She often remarked that during this period Severo Ochoa separated husband and wife in the laboratory to ensure that she would be viewed as an independent researcher in her own right, and not merely Eladio's wife.

Return to the CIB (1967–1977)

Upon returning to Spain in September 1967, she rejoined the CIB, where she founded her first research group with her husband. There, they began their systematic genetic analysis of a bacterial virus, the phage *Phi29*, although shortly after Eladio Viñuela created a new line of research on African swine fever virus. From then on, Margarita independently oversaw the bacteriophage research line. Among other findings, she characterized RNA polymerase, the viral enzyme that transcribes viral DNA to RNA, forming the basis for an entire line of research. Moreover, she discovered that the double-stranded linear DNA of the virus contained a specific protein, p3, bound at one end of either strand, that acted as a starting point for viral genome replication. Later, while working at the CBMSO, Margarita and her team discovered the viral enzyme responsible for replication of the viral genome: DNA polymerase of *Phi29*.

During the first 10 years of her career as an independent researcher at the CIB, she contributed to the creation of Spain's first department of molecular biology. She was also key figure, together with her husband and other leading researchers, in the creation of the CBM (now CBMSO), Spain's first molecular biology research center, to which she definitively transferred in 1977.

Eladio Viñuela, Antonio Talavera, Jesús Ávila, José Gómez-Acebo, Lola Hermoso, Roberto Parrilla, Juanjo López Fando, Matilde Salinas, **Margarita Salas**, Enrique Méndez, and José Luis Rodríguez Candela, among others (CIB, 1968).

There, for several decades up until her death, she led one of the most important and productive research groups in the country, and oversaw the training of tens of researchers, many of whom are currently directing leading research groups and research centers. Her wide-reaching and outstanding scientific career earned her numerous national and international scientific prizes and awards. She was the first Spanish member of the American Academy of Sciences and the first female researcher to enter the Royal Spanish Academy. She has been awarded honorary doctorates by more than a dozen universities, and was a recipient of the King Jaime I Prize, the Santiago Ramón y Cajal National Research Prize, and the UNESCO L'Oreal Award for Women in Science. In 2017 she received the Nature Award for Mentoring in Science. She was awarded her last international prize in June 2019 from the European Patent and Trademark Office, which presented her with the 2019 European Inventor Award in two categories: Popular Prize and Lifetime Achievement Award.

Role of women in science

She never neglected the dissemination of science, participating in interviews and public events defending basic research and the role of women in science. She herself recognized that she had not always been aware of gender biases in research. When she was, she started to explain how she had experienced sexism at the beginning of her career and highlighted her role as a woman of science, serving as a model for many girls and young women with a scientific vocation.

The path she followed, as both a person and a scientist, has made her one of the most important female scientists in the history of Spain and, without doubt, the most well known, with streets,

schools, and institutes named in her honour. Now, she will also lend her name to a research center, the CIB, part of the CSIC, the scientific research institution in which she spent her entire career. The **Centro de Investigaciones Biológicas Margarita Salas** proudly bears her name since November 21.

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Spontaneous and Enzymatically Catalyzed Anomerization of Glucose 6-Phosphate and Anomeric Specificity of Related Enzymes*

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Publication of Margarita Salas' first scientific discovery, obtained during her PhD in Alberto Sols' group at CIB

My thesis with Margarita Salas: between the CIB and the CBM

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It was so long ago that not even the bricks on the façade had started to fall. It was a spring morning in 1977 when I first climbed the stairs of the Centro de Investigaciones Biológicas at Velázquez 144. I had just completed a course in Molecular Genetics taught by Marta Rodríguez Inciarte at the Faculty of Biology of the Universidad Complutense de Madrid.

The Center for Biological Research, at Velázquez 144.

Marta was my mentor, and the person who convinced Margarita to let me join her laboratory. During her doctoral thesis, directed by Eladio Viñuela, Marta had generated the second ever-published complete restriction map of a viral genome, ordering the five restriction fragments that the *EcoRI* enzyme generated from the 18 kb of the *Phi29* genome! This had not been a trivial task, since 'the enzyme' (the sole restriction enzyme available at that moment) had to be purified through the use of fermenters that enabled the large-scale growth of the enzyme-producing bacterium. That's how I met José María Lázaro, the laboratory technician who oversaw this task, the best protein purifier I've ever met, and a faithful collaborator who worked with Margarita until his retirement a few years ago. As soon as I arrived at the laboratory, which I'll describe in detail shortly, Marta threw a lead apron on me and told me to keep my eyes open and soak up all the necessary know-how about phage purification with ^{32}P-labelled DNA. Labelling was performed using 5 mCi in a single experiment. I opened my very pores, not just my eyes!

The laboratory was located in the "Viñuelas wing",